



---

Year: 2019

---

## ACE-inhibitors: a preventive measure for bone flap resorption after autologous cranioplasty?

Schütz, Alessa ; Murek, Michael ; Stieglitz, Lennart Henning ; Bernasconi, Corrado ; Vulcu, Sonja ; Beck, Jürgen ; Raabe, Andreas ; Schucht, Philippe

**Abstract:** OBJECTIVE Decompressive craniectomy (DC) is an established treatment for refractory intracranial hypertension. It is usually followed by autologous cranioplasty (AC), the reinsertion of a patient's explanted bone flap. A frequent long-term complication of AC is bone flap resorption (BFR), which results in disfigurement as well as loss of the protective covering of the brain. This study investigates risk factors for BFR after AC, including medical conditions and antihypertensive drug therapies, with a focus on angiotensin-converting enzyme inhibitors (ACEIs), which have been associated with a beneficial effect on bone healing and bone preservation in orthopedic, osteoporosis, and endocrinology research. METHODS In this single-center, retrospective study 183 consecutive cases were evaluated for bone flap resorption after AC. Information on patient demographics, medical conditions, antihypertensive therapy, and BFR-defined as an indication for revision surgery established by a neurosurgeon based on clinical or radiographic assessments-was collected. A Kaplan-Meier analysis of time from AC to diagnosis of BFR was performed, and factors associated with BFR were investigated using the log-rank test and Cox regression. RESULTS A total of 158 patients were considered eligible for inclusion in the data analysis. The median follow-up time for this group was 2.2 years (95% CI 1.9-2.5 years). BFR occurred in 47 patients (29.7%), with a median time to event of 3.7 years (95% CI 3.3-4.1 years). An ACEI prescription was recorded in 57 cases (36.1%). Univariate Kaplan-Meier analysis and the log-rank test revealed that ACEI therapy (2-year event free probability [EFP]  $83.8\% \pm 6.1\%$  standard error vs  $63.9\% \pm 5.6\%$ ,  $p = 0.02$ ) and ventriculoperitoneal (VP) shunt treatment (2-year EFP  $86.9\% \pm 7.1\%$  vs  $66\% \pm 5.0\%$ ,  $p = 0.024$ ) were associated with a lower probability of BFR. Multiple Cox regression analysis showed ACEI therapy (HR 0.29,  $p = 0.012$ ), VP shunt treatment (HR 0.278,  $p = 0.009$ ), and male sex (HR 0.500,  $p = 0.040$ ) to be associated with a lower risk for BFR, whereas bone fragmentation (HR 1.92,  $p = 0.031$ ) was associated with a higher risk for BFR. CONCLUSIONS Hypertensive patients treated with ACEIs demonstrate a lower rate of BFR than patients treated with other hypertensive medications and nonhypertensive patients. Our results are in line with previous reports on the positive influence of ACEIs on bone healing and preservation. Further analysis of the association between ACEI treatment and BFR development is needed and will be evaluated in a multicenter prospective trial.

DOI: <https://doi.org/10.3171/2018.6.JNS172605>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-160412>

Journal Article

Published Version

Originally published at:

Schütz, Alessa; Murek, Michael; Stieglitz, Lennart Henning; Bernasconi, Corrado; Vulcu, Sonja; Beck, Jürgen; Raabe, Andreas; Schucht, Philippe (2019). ACE-inhibitors: a preventive measure for bone flap resorption after autologous cranioplasty? *Journal of Neurosurgery*, 131(5):1607-1614.  
DOI: <https://doi.org/10.3171/2018.6.JNS172605>

## ACE-inhibitors: a preventive measure for bone flap resorption after autologous cranioplasty?

\*Alessa Schütz, MD,<sup>1</sup> Michael Murek, MD,<sup>1</sup> Lennart Henning Stieglitz, MD,<sup>2</sup>  
Corrado Bernasconi, MD, PhD,<sup>3</sup> Sonja Vulcu, MD,<sup>1</sup> Jürgen Beck, MD,<sup>1</sup> Andreas Raabe, MD,<sup>1</sup> and  
Philippe Schucht, MD<sup>1</sup>

Departments of <sup>1</sup>Neurosurgery and <sup>3</sup>Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland; and  
<sup>2</sup>Department of Neurosurgery, Zurich University Hospital, Zurich, Switzerland

**OBJECTIVE** Decompressive craniectomy (DC) is an established treatment for refractory intracranial hypertension. It is usually followed by autologous cranioplasty (AC), the reinsertion of a patient's explanted bone flap. A frequent long-term complication of AC is bone flap resorption (BFR), which results in disfigurement as well as loss of the protective covering of the brain. This study investigates risk factors for BFR after AC, including medical conditions and antihypertensive drug therapies, with a focus on angiotensin-converting enzyme inhibitors (ACEIs), which have been associated with a beneficial effect on bone healing and bone preservation in orthopedic, osteoporosis, and endocrinology research.

**METHODS** In this single-center, retrospective study 183 consecutive cases were evaluated for bone flap resorption after AC. Information on patient demographics, medical conditions, antihypertensive therapy, and BFR—defined as an indication for revision surgery established by a neurosurgeon based on clinical or radiographic assessments—was collected. A Kaplan-Meier analysis of time from AC to diagnosis of BFR was performed, and factors associated with BFR were investigated using the log-rank test and Cox regression.

**RESULTS** A total of 158 patients were considered eligible for inclusion in the data analysis. The median follow-up time for this group was 2.2 years (95% CI 1.9–2.5 years). BFR occurred in 47 patients (29.7%), with a median time to event of 3.7 years (95% CI 3.3–4.1 years). An ACEI prescription was recorded in 57 cases (36.1%). Univariate Kaplan-Meier analysis and the log-rank test revealed that ACEI therapy (2-year event free probability [EFP]  $83.8\% \pm 6.1\%$  standard error vs  $63.9\% \pm 5.6\%$ ,  $p = 0.02$ ) and ventriculoperitoneal (VP) shunt treatment (2-year EFP  $86.9\% \pm 7.1\%$  vs  $66\% \pm 5.0\%$ ,  $p = 0.024$ ) were associated with a lower probability of BFR. Multiple Cox regression analysis showed ACEI therapy (HR 0.29,  $p = 0.012$ ), VP shunt treatment (HR 0.278,  $p = 0.009$ ), and male sex (HR 0.500,  $p = 0.040$ ) to be associated with a lower risk for BFR, whereas bone fragmentation (HR 1.92,  $p = 0.031$ ) was associated with a higher risk for BFR.

**CONCLUSIONS** Hypertensive patients treated with ACEIs demonstrate a lower rate of BFR than patients treated with other hypertensive medications and nonhypertensive patients. Our results are in line with previous reports on the positive influence of ACEIs on bone healing and preservation. Further analysis of the association between ACEI treatment and BFR development is needed and will be evaluated in a multicenter prospective trial.

<https://thejns.org/doi/abs/10.3171/2018.6.JNS172605>

**KEYWORDS** bone flap resorption; aseptic osteolysis; craniectomy; autologous cranioplasty; ACE-inhibitors; bone preservation; surgical technique

**D**ECOMPRESSIVE craniectomy (DC) is a well-established neurosurgical procedure in the treatment of refractory intracranial hypertension. Although DC is highly effective and generally regarded as a life-saving procedure, it remains an invasive surgery with an

elevated risk for complications.<sup>18</sup> To restore the bony coverage of the brain and avoid clinical impairments like the “syndrome of the trephined,”<sup>23</sup> DC is usually followed by a second surgery to cover the defect once the brain swelling has regressed. Many options exist as to the timing and

**ABBREVIATIONS** AC = autologous cranioplasty; ACEI = angiotensin-converting enzyme inhibitor; BFR = bone flap resorption; CI = confidence interval; CVI = cerebrovascular ischemia; DC = decompressive craniectomy; EFP = event-free probability; HR = hazard ratio; ICH = intracerebral hemorrhage; IQR = interquartile range; mTTE = median time to event; PTH = parathyroid hormone; RAAS = renin-angiotensin-aldosterone system; RR = relative risk; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury; VP = ventriculoperitoneal.

**SUBMITTED** November 29, 2017. **ACCEPTED** June 11, 2018.

**INCLUDE WHEN CITING** Published online November 23, 2018; DOI: 10.3171/2018.6.JNS172605.

\* A.S. and M.M. contributed equally to this work and share first authorship.

procedure for covering the bony defect,<sup>10,27</sup> but autologous cranioplasty (AC)—the reinsertion of the explanted, cryoconserved bone flap—is the most common one.<sup>10</sup>

A frequently observed long-term complication of AC is bone flap resorption (BFR), an aseptic, osteolytic process leading to significant disintegration of the reimplanted bone in up to 54.4% of pediatric patients<sup>4,21,25</sup> and up to 30.4% of patients in mixed cohorts.<sup>5,8,9,17,22,35</sup> BFR can lead to visible and palpable, aesthetically disfiguring defects, and in its advanced form it results in a loss of the bony coverage of the brain. Revision surgery with implantation of a synthetic bone flap is required in severe cases of BFR.

In recent decades there has been a growing interest in identification of potential strategies for lowering BFR rates, avoiding revision surgery, and preventing possible surgical complications. Previous studies have found risk factors such as fragmentation of the bone flap,<sup>5,8,21,33</sup> younger age,<sup>4,5,8,21</sup> longer time between DC and AC,<sup>5,33</sup> ventriculoperitoneal (VP) shunt implantation,<sup>4,22</sup> and larger bone flap size<sup>32</sup> to be associated with higher rates of BFR. The pathophysiological mechanism of BFR, however, remains unclear, and no preventive measures have been identified to date.

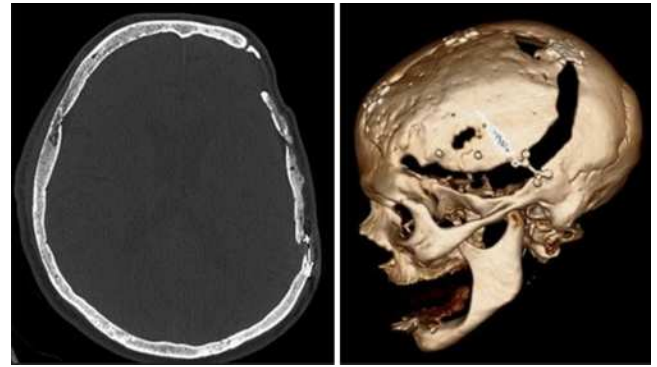
In addition, research in the fields of orthopedics, osteoporosis, and endocrinology has identified a beneficial effect of angiotensin-converting enzyme inhibitors (ACEIs) on bone preservation and bone healing. These medications have been found to be associated with an increased bone mineral density,<sup>26</sup> improved osteoporosis,<sup>34</sup> and bone healing,<sup>39</sup> as well as reduced fracture risk.<sup>28,31</sup> They prevent the conversion of angiotensin I into angiotensin II, which increases calcium metabolism and activates osteoclasts responsible for bone resorption.<sup>34</sup> To verify whether these findings could be applied to autologous bone flaps we set out to investigate a putative effect of ACEIs on BFR development.

## Methods

### Study Design and Patient Cohort

We performed a single-center, retrospective analysis of 183 consecutive cases in which patients received AC after DC at the Department of Neurosurgery, Inselspital, University Hospital Bern, Switzerland, between June 2003 and August 2015. Data were collected and managed using REDCap, a secure, web-based electronic data capture tool<sup>15</sup> in a retrospective review of hospital records and CT scans. Patients with DC, followed by primary implantation of the autologous bone flap (AC) were included in the study. Patients who did not show up for at least 1 follow-up visit or never received a follow-up CT scan were considered ineligible and were excluded from the analysis. Subjects who received a synthetic bone flap within 1 year after AC for reasons other than BFR were also excluded from the study.

Institutional protocol required a postoperative follow-up visit with CT scan 6 weeks after surgery. Further follow-up visits were scheduled depending on the clinical or radiographic findings of the initial follow-up or if requested by the patient or his or her family practitioner.



**FIG. 1.** Left: CT scan showing BFR 4.9 years after bone flap reimplantation. Right: 3D CT reconstruction of skull with BFR (same case).

The last point of follow-up was defined as the date of BFR diagnosis by clinical or radiographic examination. For patients with no documented BFR, the clinical results of the most recent follow-up visit or available CT scan defined the follow-up time.

### Definition of Bone Flap Resorption

Bone flap resorption (BFR) was defined at the point of necessity of surgical revision, as diagnosed after a clinical examination or viewing of CT scans by the treating neurosurgeon (Fig. 1).

Bone flap size was estimated using the maximum anteroposterior (B) and craniocaudal diameters (b) from lateral scout images with the formula  $A = \pi/4 \times B \times b$ , as proposed by Dünisch et al.<sup>8</sup> and Ewald et al.<sup>9</sup>

### Decompressive Craniectomy

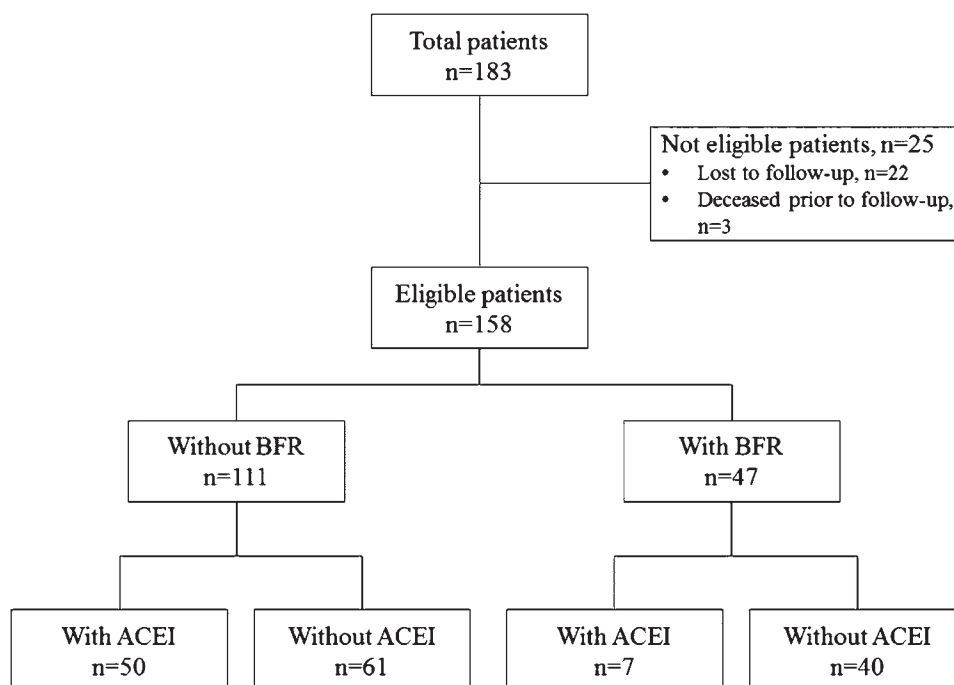
DC was performed according to a previously published protocol<sup>14</sup> with the cross midline skin incision technique to facilitate cranioplasty and a DC diameter of at least 150 mm. The dura was opened in a stellate form, folded back on the exposed brain, and covered with a layer of Surgicel (Ethicon, Inc.). The explanted, sterile bone flap was cryoconserved at  $-80^{\circ}\text{C}$ .

### Autologous Cranioplasty

The sterile, cryoconserved bone flaps were thawed for reimplantation at room temperature. In 21 (13.3%) patients multiple 1-mm-diameter holes were drilled into the bone flap in order to prevent the build-up of epidural fluid collections in combination with a subcutaneous drainage. The number of holes drilled was determined according to the individual neurosurgeon's preference and ranged between 3 and 52 per bone flap (mean 8 holes). Meticulous dissection of the myocutaneous flap and exposure of bony margins followed. The bone flap fixation method—i.e., titanium plates and screws (low profile, Synthes), titanium clamps (Craniofix, Braun Medical AG), or cranial sutures (nonabsorbable Surgilon braided nylon, Covidien)—was based on the neurosurgeon's preference.

### Recorded Variables

The following variables were extracted from clinical



**FIG. 2.** Flowchart showing development of BFR in patients with or without antihypertensive therapy with ACEIs.

records and entered into our database: patient sex, age, admission diagnosis leading to DC, dates of surgery (including DC and AC), number of bone fragments and size, VP shunt placement, diagnosis of arterial hypertension and diabetes, nicotine consumption, antihypertensive therapy with ACEIs, and the date of the last follow-up visit. The presence of BFR was documented in clinical records based on clinical evaluation or after evaluation of CT scans.

Patients who declined revision surgery despite an indication as determined by the treating neurosurgeon were included in the study and categorized as patients with BFR.

### Statistical Analysis

Baseline characteristics of patients with and without BFR were analyzed descriptively and compared using the 2-sample t-test with pooled variances for continuous variables and Fisher's exact test for categorical variables. A Kaplan-Meier analysis of time from AC to diagnosis of BFR was performed and putative predictors associated with BFR were investigated using the log-rank test. A multivariable Cox proportional hazards model was fitted to delineate the specific influence of ACEI on BFR after accounting for previously mentioned predictors. Median follow-up time and results in the time-to-event analysis were presented and compared as median time-to-event (mTTE) calculated using the reversed Kaplan-Meier estimate<sup>30</sup> and 2-year event-free probabilities (EFPs). Results from Cox regression analysis were presented with hazard ratios (HRs) and 95% confidence intervals (CIs). Patients missing data on any of the predictors and patients without follow-up were excluded from the analysis. To avoid unnecessary radiation exposure, only patients

with suspected or clinically confirmed BFR received CT follow-up. To exclude the bias of pure clinical follow-up in patients with indication for BFR, a sensitivity analysis was conducted considering only CT follow-up. A p value of < 0.05 was considered statistically significant. Statistical analysis was performed using standard commercial software (IBM SPSS Statistics for Windows, version 21.0, IBM Corp.).

### Ethics

Approval was granted by the local ethics committee (Kantonale Ethikkommission Bern, Switzerland).

## Results

### Patient Characteristics

During June 2003 to August 2015 a total of 183 patients (age range 4–81 years) who received AC after DC were assessed for study eligibility. A total of 25 patients (13.7%) did not meet the eligibility criteria; 22 of these patients had been lost to follow-up after AC and 3 patients had died before any follow-up (Fig. 2).

The baseline characteristics of the 158 eligible patients are summarized in Table 1. The median time between DC and AC was 70 days (interquartile range [IQR] 46–103.25 days), and the median follow-up time was 2.2 years (95% CI 1.9–2.5 years). The patients' mean age at the time of AC was 43.6 years (IQR 31.5–56 years), and 101 (63.9%) were male. The most common diagnosis resulting in DC was traumatic brain injury (TBI, n = 62, 39.2%) followed by cerebrovascular ischemia (CVI, n = 35, 22.2%) and intracerebral hemorrhage (ICH, n = 25, 15.8%). Twenty-eight patients (17.7%) received a ventriculoperitoneal (VP)



**TABLE 1. Baseline patient characteristics**

Variable	All Pts (n = 158)	Pts w/o BFR (n = 111)	Pts w/ BFR (n = 47)	RR/Difference* (95% CI)	p Value
Age in yrs, mean	43.6 ± 16.3	45.3 ± 16.0	39.5 ± 16.3	5.84 (0.31–11.38)	0.039
Male sex, n (%)	101 (63.9%)	73 (65.8%)	28 (59.6%)	0.83 (0.51–1.35)	0.474
Admission diagnosis, n (%)					
ICH	25 (15.8%)	23 (20.7%)	2 (4.3%)	0.24 (0.06–0.91)	0.008
SAH	17 (10.8%)	8 (7.2%)	9 (19.1%)	1.96 (1.16–3.32)	0.046
CVI	35 (22.2%)	28 (25.2%)	7 (14.9%)	0.62 (0.30–1.25)	0.209
TBI	62 (39.2%)	41 (36.9%)	21 (44.7%)	1.25 (0.78–2.02)	0.378
SDH	6 (3.8%)	4 (3.6%)	2 (4.3%)	1.13 (0.35–3.58)	1.000
Cerebral infection	4 (2.5%)	2 (1.8%)	2 (4.3%)	1.71 (0.62–4.70)	0.583
Miscellaneous	9 (5.7%)	5 (4.5%)	4 (8.5%)	0.65 (0.30–1.41)	0.452
VP shunt, n (%)	28 (17.7%)	22 (19.8%)	6 (12.8%)	0.68 (0.32–1.44)	0.365
Time from DC to AC in mos, mean	2.7 ± 1.7	2.6 ± 1.5	2.8 ± 2.1	0.13 (–0.46 to 0.72)	0.666
Medical conditions, n (%)					
Arterial hypertension	68 (43.0%)	56 (50.5%)	12 (25.5%)	0.45 (0.26–0.81)	0.005
Diabetes mellitus	10 (6.3%)	8 (7.2%)	2 (4.3%)	0.66 (0.19–2.33)	0.724
Antihypertensive therapy, n (%)					
ACEI	57 (36.1%)	50 (45%)	7 (14.9%)	0.31 (0.15–0.65)	<0.001
Other antihypertensive drugs	46 (29.1%)	37 (33.3%)	9 (19.1%)	0.58 (0.30–1.09)	0.086
Nicotine consumption	36 (22.8%)	25 (22.5%)	11 (23.4%)	1.02 (0.79–1.3)	1.000
Size in cm <sup>2</sup> , mean	110.1 ± 22.4	112.5 ± 2.1	104.9 ± 2.6	7.6 (–0.10 to 15.35)	0.053
≥2 fragments, n (%)†	43 (29.3%)	26 (25.5%)	17 (37.8%)	1.47 (0.90–2.39)	0.096

Pts = patients; SDH = subdural hemorrhage.

Continuous values are depicted as means ± SD, discrete values as their absolute number of observations (n) and the percentage of the respective group; p values are from 2-sample t-tests for continuous variables and Fisher's exact tests for categorical variables.

\* The relative risk is presented for categorical data and the difference in the means for continuous data.

† Total n = 147, with BFR = 45, without BFR = 102.

shunt around the time of DC. Fixation methods applied were titanium clamps in 7 patients (4.4%), titanium plates and screws in 150 patients (93.8%), and sutures in 1 patient (0.6%). Arterial hypertension was documented in 68 patients (43%). In 22 (32.4%) of these 68 patients it was newly diagnosed at DC; 41 (60.3%) had documented arterial hypertension in the admissions report for DC or older medical reports, and 5 patients (7.4%) were first recorded to have arterial hypertension at AC. A prescription for an ACEI was recorded for 57 of the hypertensive patients (36.1%) during their stay for AC or at later follow-up visits. Of the 101 patients who were not treated with an ACEI, 15 (14.9%) had a recorded diagnosis of arterial hypertension. Seven (14.9%) (see Fig. 2 and Table 3) of the patients who were prescribed an ACEI developed BFR.

A total of 47 patients (29.7%) were clinically or radiologically diagnosed with BFR. Of the patients with BFR, 2 declined revision surgery despite their neurosurgeons' recommendations. Seven patients (4.4%) developed a wound infection after AC, of which none developed BFR. Two patients had surgical revision reasons other than BFR. One patient had severe dislocation of the autologous bone flap 9 years after AC, and 1 patient had an intracranial empyema 1 year and 8 months after AC. These patients were defined as having no BFR and were censored at the time of surgical revision.

## Univariate Analysis

Univariate comparison showed that patients with BFR were younger (mean age 39.5 vs 45.3 years,  $p = 0.039$ ), less likely to have arterial hypertension (relative risk [RR] 0.45, 95% CI 0.26–0.81,  $p = 0.005$ ), and less likely to be treated with ACEIs (RR 0.31, 95% CI 0.15–0.65,  $p < 0.001$ ), as well as less (RR 0.31) likely to have had an ICH (RR 0.24, 95% CI 0.06–0.91,  $p = 0.008$ ) and more (RR 1.96) frequently subarachnoid hemorrhage (SAH, RR 1.96, 95% CI 1.16–3.32,  $p = 0.046$ ) (Table 1).

Univariate Kaplan-Meier analysis revealed that ACEI therapy (2-year EFP [± standard error] 83.8% ± 6.1% vs 63.9% ± 5.6%,  $p = 0.02$ ) and VP shunt placement (2-year EFP 86.9% ± 7.1% vs 66% ± 5.0%,  $p = 0.024$ ) were associated with a lower probability of BFR (Table 2, Fig. 3).

## Cox Regression Analysis

According to multiple Cox regression analysis ACEI treatment was associated with a lower risk for BFR (HR 0.293, 95% CI 0.112–0.764,  $p = 0.012$ ), as were VP shunt placement (HR 0.278, 95% CI 0.106–0.724,  $p = 0.009$ ) and male sex (HR 0.500, 95% CI 0.258–0.969,  $p = 0.040$ ) (Fig. 4). Fragmentation of the bone flap was associated with a higher rate of BFR (HR 1.920, 95% CI 1.061–3.477,  $p = 0.031$ ).

**TABLE 2. Results of univariate Kaplan-Meier analysis with log-rank test**

Variable	2-yr EFP* (%)	mTTE (yrs)	mTTE, 95% CI	p Value
Age in yrs				0.632
0–20	55.6 ± 11.7	4.2	0.0–8.8	
21–40	65.7 ± 8.5	3.8	2.1–5.5	
41–60	74.9 ± 6.6	3.7	2.4–5.0	
61–80	79.7 ± 9.1	NR	NR	
Sex				0.075
Male	74.1 ± 5.1	3.9	3.5–4.4	
Female	63.4 ± 7.6	2.7	2.3–3.1	
VP shunt				0.024
Yes	86.9 ± 7.1	4.2	NR	
No	66.0 ± 5.0	3.6	2.5–4.7	
Time from DC to AC in mos				0.551
≤2	72.9 ± 6.7	4.2	2.0–6.4	
2.1–4	64.0 ± 6.8	3.4	2.1–4.8	
4.1–6	72.9 ± 13.5	3.9	NR	
>6.1	90.0 ± 9.5	3.6	0.0–8.1	
ACEI				0.02
Yes	83.8 ± 6.1	NR	NR	
No	63.9 ± 5.6	3.6	2.4–4.9	
Bone flap size in cm <sup>2</sup>				0.52
≤70	38.1 ± 19.9	1.9	0.1–3.7	
71–90	90.9 ± 8.7	3.7	2.6–4.8	
91–110	68.8 ± 9.2	3.9	2.5–5.4	
≥110	66.3 ± 6.0	3.4	NR	
Fragments				0.488
≥2	65.3 ± 7.8	5.5	1.8–9.2	
<2	69.1 ± 5.6	3.8	3.6–4.8	

2-yr EFP = 2-year event free probability; mTTE = median time to event; NR = not reached.

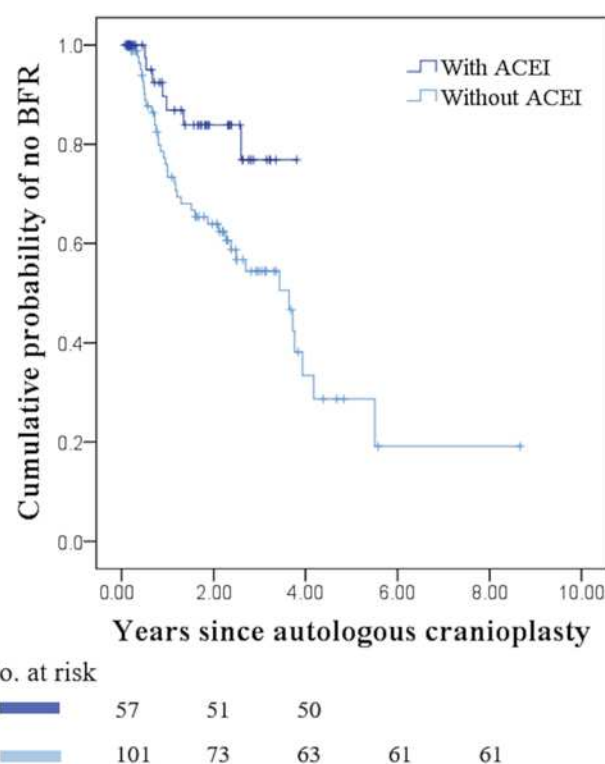
\* Presented with standard error.

A sensitivity analysis considering only CT follow-up and omitting clinical follow-up data continued to show a reduced risk for BFR in patients with ACEIs (HR 0.299,  $p = 0.01$ ), as well as an elevated risk in patients with multiple fragmentation of the bone flap (HR 1.794,  $p = 0.042$ ).

## Discussion

### Definition of Bone Flap Resorption

As of this writing, there has been no consensus on a definition for the term “bone flap resorption” (BFR). Ewald et al.<sup>9</sup> and Dünisch et al.<sup>8</sup> defined a type II bone flap necrosis as a circumscribed or complete lysis of both the tabula interna and the tabula externa with the requirement of surgical revision. Stieglitz et al.<sup>35</sup> categorized BFR using a scoring system, with major resorption requiring a second surgery. We limited the definition of BFR to the indication for revision surgery. In our study, 47 patients (29.7%) were diagnosed with BFR, which appears to be in line with rates previously reported in the literature (Table 3).



**FIG. 3.** Kaplan-Meier analysis of patients with and without ACEI treatment and number of patients at risk after each time interval. Tick marks indicate censored events.

### Arterial Hypertension and BFR

Arterial hypertension was a frequent comorbidity in our study (affecting 43% of patients, with 97.1% of these hypertensive patients receiving antihypertensive medication) because hypertensive patients have a severely heightened risk for cerebrovascular incidents such as CVI or ICH.<sup>1,23</sup> Analysis of baseline characteristics showed that a majority of the patients with BFR were admitted with TBI ( $n = 21$ , 44.7%) and SAH ( $n = 9$ , 19.1%), and that the majority of patients without BFR were admitted due to TBI ( $n = 41$ , 36.9%) or CVI ( $n = 28$ , 25.2%). More patients suffered from ICH than from SAH ( $n = 25$ , 15.8% vs  $n = 17$ , 10.8%). In a prospective study involving elderly females, Cappuccio et al.<sup>6</sup> showed that hypertension is associated with an abnormal calcium metabolism. It leads to increased urinary calcium excretion, secondary activation of the parathyroid gland, and increased calcium mobilization from bone. In our study, 68 patients had a diagnosis of arterial hypertension, and 12 (17.6%) of these patients developed BFR. Sixty-six (97.1%) of the 68 patients with arterial hypertension received antihypertensive medication, and 57 (83.8%) of these 68 received an ACEI.

However, we cannot assume that the possible benefit of ACEI therapy with respect to development of BFR is based solely on normalization of blood pressure. According to the literature, not all antihypertensive drugs beneficially affect osteoporosis and bone mineralization, as they differ in the way they work to reduce blood pressure.<sup>19,38</sup> Previous findings suggest a beneficial effect of

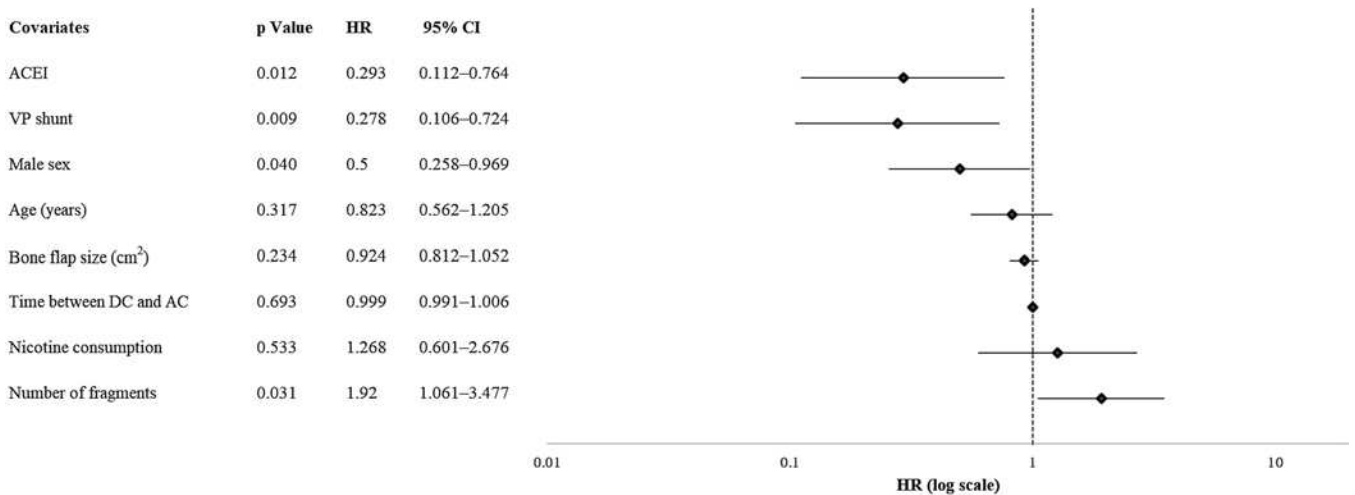


FIG. 4. Results and plot of hazard ratios from a multiple Cox regression analysis on a logarithmic scale.

ACEI therapy on bone preservation by direct alteration of the RAAS.<sup>12,16</sup>

### The Renin-Angiotensin-Aldosterone System and Bone Metabolism

In recent years, multiple studies conducted in orthopedic, osteoporosis, and endocrinology research have associated ACEIs with a beneficial effect on bone preservation and bone healing.<sup>26,28,31,34,39</sup> In animal studies, activation of the renin-angiotensin-aldosterone system (RAAS), a system that regulates blood volume and pressure through multiple hormones and enzymes systemically and locally, seems to induce osteoporosis,<sup>2</sup> which was attenuated by ACEI administration.<sup>34</sup> Furthermore, it has been possible to increase bone resorption and decrease bone mineral density by administration of angiotensin II in a mouse model,<sup>2</sup> while local injection of ACEI into the area of tibial fractures has resulted in improved bone healing in a rat model.<sup>39</sup> In human studies, a 1-hour infusion of angiotensin II, alone or in combination with human parathyroid hormone (PTH), has been shown to inhibit RAAS and calcium metabolism,<sup>13</sup> whereas ACEI therapy was associated with an increased bone mass<sup>26</sup> and a decreased fracture risk.<sup>13,28,31,37</sup>

Previous studies have explained these effects by showing that angiotensin II indirectly stimulates osteoclast formation,<sup>2</sup> leads to decreased ionic calcium and increased PTH levels,<sup>13</sup> and directly affects local tissue-specific RAAS also found within bone tissue.<sup>12,16</sup> Administration of an ACEI prevents the enzymatic conversion of angiotensin I into angiotensin II, thus preventing the catabolic effect of angiotensin II, thus resulting in decreased bone resorption. Furthermore, ACEIs have been shown to increase bone mass in hypertensive women with a specific polymorphism of the *ACE* gene due to a stronger inhibitory effect by the ACEI and further decrease of angiotensin II levels.<sup>26</sup>

Of the 68 (Table 1) hypertensive patients in our study, 57 (84%) were following a regimen of ACEI therapy. We identified these patients as having a lower rate of BFR.

Our results are in line with findings in the literature,

showing how ACEIs can positively affect osteogenesis by alteration of the RAAS in hypertensive patients. This implicates a potential preventive measure against BFR, which could be offered to patients undergoing AC. However, our investigation was limited to a prescription for an ACEI in patients with a known arterial hypertension. Their effects on BFR in normotensive patients therefore remain unclear. For future studies, we recommend considering all drugs acting on the RAAS and their potential effects on bone metabolism, as well as investigating the effects of ACEIs on BFR in normotensive patients.

### Sex, VP Shunts, and Bone Fragmentation

In our analysis, we found male sex to be associated with lower BFR rates. Previous studies did not identify patient sex as a risk factor for BFR in pediatric and mixed cohorts.<sup>4,8</sup> However, prior studies suggest an altered bone metabolism in postmenopausal women due to changes in estrogen levels affecting bone metabolism (e.g., resulting in lower bone mineral density<sup>11</sup> or complications in the healing of fractures such as clavicular or femoral neck fractures<sup>24,29</sup>).

Additionally, our analysis found VP shunt placement to be associated with lower BFR rates. In previous studies, shunt-dependent hydrocephalus has been reported to be a risk factor for BFR,<sup>4,22,25</sup> the reason for this however is not established. Overall, the impact of hydrocephalus and VP shunts on BFR rates remains unclear.

Increasing fragmentation of the bone flap was associated with higher BFR rates, confirming results found in previous reports.<sup>5,8,21,33</sup> It has been theorized that fragmentation leads to a nutritional deficit of the bone flap<sup>8</sup> and disturbance of later angiogenesis and the survival of the graft.<sup>5</sup>

### Limitations

Given that this was a single-institution study, our cohort size and event numbers were limited. Because our institutional protocol only required a 6-week postoperative fol-



**TABLE 3. Review of resorption rates found in the literature, as well as mean or median age and follow-up documented**

Authors & Year	Total BFR Rate (%)	Follow-Up (mos)*	Age (yrs)*
Bowers et al., 2013	50	37.9	6.2
Brommeland et al., 2015	19.7	9.9	31
Dünisch et al., 2013	22.8	11	48.6
Ewald et al., 2014	22.8	9	54.3
Honeybul & Ho, 2016	20.9	NA	36
Martin et al., 2014	81.8	83	4.9 vs 17.4†
Mracek et al., 2015	20	11	49
Pechmann et al., 2015	50	29.4	8.5
Piedra et al., 2013	17	24.2	29.5
Schoekler & Trummer, 2014	8	NA‡	46
Schuss et al., 2013	4	45	45
Stieglitz et al., 2015	30.4	21.6	46.2
Present study overall	29.7	26.1	43.6
w/ ACEI	12.3	20.5	53.1
w/o ACEI	39.6	29.2	38.2

NA = not available.

\* Mean or median values, as documented in cited source.

† Analysis of 2 patient subgroups (age &lt;15 years vs 15–18 years).

‡ Routine follow-up was performed 6 months after bone flap reimplantation.

low-up visit, a minority of patients did not receive further follow-up evaluations. This may be because they or their caregivers did not consider additional follow-up necessary, or it may be due to other unknown reasons. Intraoperative placement of multiple perforations in the bone flap and the fixation method were not standardized. Neither were duration, dosage, or combination of drug therapy. In the literature an elevated risk for osteoporosis and fractures have been found to be associated with many medical and metabolic factors (e.g., increasing age, steroid therapy, hormonal factors including menopause, amenorrhea, hyperthyroidism, hyperadrenocorticism and hypogonadism) as well as lifestyle factors, such as low physical activity, nicotine or alcohol consumption, low body weight, or low dietary calcium and vitamin D intake.<sup>7</sup> In recent years interest has risen as to the use of osteoinductive factors such as bone morphogenetic proteins (BMPs), which have been applied in orthopedic surgery to improve bone healing and enhance spinal fusion.<sup>20</sup> However, to our knowledge BMPs have not been applied in autologous cranioplasty. Apart from patient age and nicotine consumption, which were not significant in our analysis, we did not assess any of these factors.

## Conclusions

ACEI therapy appears to decrease the risk of BFR after AC in hypertensive patients (76% relative risk reduction). This finding is in line with previous reports on the positive influence of ACEIs on bone healing and preservation. ACEI therapy may thus be considered as the antihypertensive treatment of choice in patients who have undergone AC. Further analysis of the association between ACEI

and BFR development is needed and will be evaluated in the Swiss Prospective Autologous Bone Flap Resorption Study (SPARS), a multicenter prospective trial.<sup>36</sup>

## References

1. Ariesen MJ, Claus SP, Rinkel GJ, Algra A: Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke* **34**:2060–2065, 2003
2. Asaba Y, Ito M, Fumoto T, Watanabe K, Fukuhara R, Takeshita S, et al: Activation of renin-angiotensin system induces osteoporosis independently of hypertension. *J Bone Miner Res* **24**:241–250, 2009
3. Ashayeri K, M Jackson E, Huang J, Brem H, R Gordon C: Syndrome of the trephined: a systematic review. *Neurosurgery* **79**:525–534, 2016
4. Bowers CA, Riva-Cambrin J, Hertzler DA II, Walker ML: Risk factors and rates of bone flap resorption in pediatric patients after decompressive craniectomy for traumatic brain injury. *J Neurosurg Pediatr* **11**:526–532, 2013
5. Brommeland T, Rydning PN, Pripp AH, Helseth E: Cranioplasty complications and risk factors associated with bone flap resorption. *Scand J Trauma Resusc Emerg Med* **23**:75, 2015
6. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA: High blood pressure and bone-mineral loss in elderly white women: a prospective study. *Lancet* **354**:971–975, 1999
7. Dantas IA, Yiannakopoulos CK: Risk factors and prevention of osteoporosis-related fractures. *J Musculoskelet Neuronal Interact* **7**:268–272, 2007
8. Dünisch P, Walter J, Sakr Y, Kalff R, Waschke A, Ewald C: Risk factors of aseptic bone resorption: a study after autologous bone flap reinsertion due to decompressive craniotomy. *J Neurosurg* **118**:1141–1147, 2013
9. Ewald C, Duenisch P, Walter J, Götz T, Witte OW, Kalff R, et al: Bone flap necrosis after decompressive hemicraniectomy for malignant middle cerebral artery infarction. *Neurocrit Care* **20**:91–97, 2014
10. Feroze AH, Walmsley GG, Choudhri O, Lorenz HP, Grant GA, Edwards MS: Evolution of cranioplasty techniques in neurosurgery: historical review, pediatric considerations, and current trends. *J Neurosurg* **123**:1098–1107, 2015
11. Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD: Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. *J Bone Miner Res* **11**:337–349, 1996
12. Gebru Y, Diao TY, Pan H, Mukwaya E, Zhang Y: Potential of RAS inhibition to improve metabolic bone disorders. *BioMed Res Int* **2013**:932691, 2013
13. Grant FD, Mandel SJ, Brown EM, Williams GH, Seely EW: Interrelationships between the renin-angiotensin-aldosterone and calcium homeostatic systems. *J Clin Endocrinol Metab* **75**:988–992, 1992
14. Güresir E, Vatter H, Schuss P, Oszvald A, Raabe A, Seifert V, et al: Rapid closure technique in decompressive craniectomy. *J Neurosurg* **114**:954–960, 2011
15. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* **42**:377–381, 2009
16. Hatton R, Stimpel M, Chambers TJ: Angiotensin II is generated from angiotensin I by bone cells and stimulates osteoclastic bone resorption in vitro. *J Endocrinol* **152**:5–10, 1997
17. Honeybul S, Ho KM: Cranioplasty: morbidity and failure. *Br J Neurosurg* **30**:523–528, 2016
18. Kurland DB, Khaladj-Ghom A, Stokum JA, Carusillo B, Karimy JK, Gerzanich V, et al: Complications associated with decompressive craniectomy: a systematic review. *Neurocrit Care* **23**:292–304, 2015

19. Lykissas M, Gkias I: Use of recombinant human bone morphogenetic protein-2 in spine surgery. **World J Orthop** **8**:531–535, 2017
20. Lynn H, Kwok T, Wong SY, Woo J, Leung PC: Angiotensin converting enzyme inhibitor use is associated with higher bone mineral density in elderly Chinese. **Bone** **38**:584–588, 2006
21. Martin KD, Franz B, Kirsch M, Polanski W, von der Hagen M, Schackert G, et al: Autologous bone flap cranioplasty following decompressive craniectomy is combined with a high complication rate in pediatric traumatic brain injury patients. **Acta Neurochir (Wien)** **156**:813–824, 2014
22. Mracek J, Hommerova J, Mork J, Richt P, Priban V: Complications of cranioplasty using a bone flap sterilised by autoclaving following decompressive craniectomy. **Acta Neurochir (Wien)** **157**:501–506, 2015
23. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al: Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. **Lancet** **376**:112–123, 2010
24. Parker MJ, Raghavan R, Gurusamy K: Incidence of fracture-healing complications after femoral neck fractures. **Clin Orthop Relat Res** **458**:175–179, 2007
25. Pechmann A, Anastasopoulos C, Korinthenberg R, van Velthoven-Wurster V, Kirschner J: Decompressive craniectomy after severe traumatic brain injury in children: complications and outcome. **Neuropediatrics** **46**:5–12, 2015
26. Pérez-Castrillón JL, Silva J, Justo I, Sanz A, Martín-Luquero M, Igea R, et al: Effect of quinapril, quinapril-hydrochlorothiazide, and enalapril on the bone mass of hypertensive subjects: relationship with angiotensin converting enzyme polymorphisms. **Am J Hypertens** **16**:453–459, 2003
27. Piedra MP, Ragel BT, Dogan A, Coppa ND, Delashaw JB: Timing of cranioplasty after decompressive craniectomy for ischemic or hemorrhagic stroke. **J Neurosurg** **118**:109–114, 2013
28. Rejnmark L, Vestergaard P, Mosekilde L: Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: a nationwide case-control study. **J Hypertens** **24**:581–589, 2006
29. Robinson CM, Court-Brown CM, McQueen MM, Wakefield AE: Estimating the risk of nonunion following nonoperative treatment of a clavicular fracture. **J Bone Joint Surg Am** **86-A**:1359–1365, 2004
30. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. **Control Clin Trials** **17**:343–346, 1996
31. Schlienger RG, Kraenzlin ME, Jick SS, Meier CR: Use of beta-blockers and risk of fractures. **JAMA** **292**:1326–1332, 2004
32. Schoekler B, Trummer M: Prediction parameters of bone flap resorption following cranioplasty with autologous bone. **Clin Neurol Neurosurg** **120**:64–67, 2014
33. Schuss P, Vatter H, Oszvald A, Marquardt G, Imöhl L, Seifert V, et al: Bone flap resorption: risk factors for the development of a long-term complication following cranioplasty after decompressive craniectomy. **J Neurotrauma** **30**:91–95, 2013
34. Shimizu H, Nakagami H, Osako MK, Nakagami F, Kunugiza Y, Tomita T, et al: Prevention of osteoporosis by angiotensin-converting enzyme inhibitor in spontaneous hypertensive rats. **Hypertens Res** **32**:786–790, 2009
35. Stieglitz LH: The Swiss Prospective Autologous Bone Flap Resorption Study (SPARS): a multicentric approach to quantify the complication rate after reimplantation of autologous cryoconserved bone flaps. **Acta Neurochir (Wien)** **157**:1001, 2015 (Letter)
36. Stieglitz LH, Fung C, Murek M, Fichtner J, Raabe A, Beck J: What happens to the bone flap? Long-term outcome after reimplantation of cryoconserved bone flaps in a consecutive series of 92 patients. **Acta Neurochir (Wien)** **157**:275–280, 2015
37. Wiens M, Etminan M, Gill SS, Takkouche B: Effects of anti-hypertensive drug treatments on fracture outcomes: a meta-analysis of observational studies. **J Intern Med** **260**:350–362, 2006
38. Yamamoto S, Kido R, Onishi Y, Fukuma S, Akizawa T, Fukagawa M, et al: Use of renin-angiotensin system inhibitors is associated with reduction of fracture risk in hemodialysis patients. **PLoS One** **10**:e0122691, 2015
39. Zhao X, Wu ZX, Zhang Y, Gao MX, Yan YB, Cao PC, et al: Locally administered perindopril improves healing in an ovariectomized rat tibial osteotomy model. **PLoS One** **7**:e33228, 2012

## Disclosures

Dr. Shucht reports an ownership interest in Trusteddoctor.

## Author Contributions

Conception and design: Schütz, Murek, Bernasconi, Schucht. Acquisition of data: Schütz, Stieglitz. Analysis and interpretation of data: Schütz, Murek, Bernasconi. Drafting the article: Schütz, Murek, Schucht. Critically revising the article: Murek, Stieglitz, Bernasconi, Vulcu, Beck, Raabe, Schucht. Reviewed submitted version of manuscript: Murek, Stieglitz, Bernasconi, Vulcu, Beck, Raabe, Schucht. Statistical analysis: Schütz, Murek, Bernasconi. Administrative/technical/material support: Schütz. Study supervision: Beck, Schucht.

## Supplemental Information

### Previous Presentations

Portions of this work were presented in poster form at the European Association for Neurosurgical Societies (EANS) Congress 2016 in Athens, Greece, September 4–8, 2016, and the American Association for Neurological Surgeons (AANS) annual scientific meeting in Los Angeles, California, April 22–26, 2017. Oral presentations were given at the SFCNS Congress in Basel, Switzerland, September 28, 2016, and at the WFNS XVI World Congress of Neurosurgery in Istanbul, Turkey, August 24, 2017.

## Correspondence

Alessa Schütz: Bern University Hospital, Bern, Switzerland. alessa.schuetz@insel.ch.